

THE REGULATION OF APPETITE, BODY WEIGHT AND ATHLETIC FUNCTION WITH MATERIALS DERIVED FROM CITRUS VARIETIES

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TECHNICAL FIELD

The present invention relates to the use of materials derived from Citrus plants in inducing weight loss, improving physical performance and increasing muscle mass.

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19 **BACKGROUND ART**

20 It has long been known that natural and synthetic substances may facilitate weight loss

21 in those who are overweight or obese. Such substances as have found utility in this respect

22 may act by a variety of mechanisms. For example, some such substances act by mimicking the

23 effects of endogenous neurotransmitters, and are capable of directly replacing these

24 neurotransmitters in their actions on receptors. This, in turn, leads to increased activity of the

25 cells which possess the receptors. Where the receptors concerned are normally responsive to

1 the endogenous hormones adrenaline (epinephrine) and noradrenaline (norepinephrine), which
2 mediate the activities of the sympathetic nervous system, such substances are termed
3 direct-acting sympathicomimetic agents. Typical examples are the amphetamines. Other
4 substances that produce similar effects on the sympathetic nervous system do so by stimulating
5 the release of the endogenous hormones adrenaline and noradrenaline, and are thus termed
6 indirect-acting sympathicomimetic agents. Ephedrine is a typical example of an indirect-acting
7 sympathicomimetic agent. The term adrenergic may also be used, and is synonymous with the
8 term sympathicomimetic. Such substances may also be referred to as agonists, where the
9 name agonist is qualified by a descriptor of the receptor stimulated, for example, a
10 beta-agonist.

11 While the formal distinction between direct-acting and indirect-acting
12 sympathicomimetic action is clear, it is realized that many substances which act by causing
13 sympathetic stimulation do so by both mechanisms, depending on intake levels and the
14 receptors involved. Thus amphetamines act mainly directly, but also have some indirect
15 actions, while ephedrine acts indirectly, but if given in higher dosage, may also stimulate
16 receptors directly, particularly in the brain. It has been demonstrated that the main perceived
17 actions of sympathicomimetic agents depend both on their differing specificities for the various
18 receptors and on the pharmacokinetic behaviors of the agents in the body.

19 Thus the amphetamines, which are direct agents and readily cross the blood-brain
20 barrier, mainly cause central nervous system stimulation, while ephedrine, and particularly
21 pseudoephedrine, are indirect agents which do not cross the blood-brain barrier so readily, and
22 thus are mainly seen to exert peripheral effects.

23 Another class of substances of value in assisting weight loss modulates other
24 neurotransmitters, namely those involved in serotonergic systems, and particularly
25 5-hydroxytryptamine (5-HT; otherwise known as serotonin) itself. These substances, of which

1 fenfluramine and its optical isomer, dexfenfluramine, are typical, act by preventing the
2 re-uptake of serotonin into storage granules in neurones. Levels of 5-HT in the synaptic gap
3 thus remain elevated for longer periods, exciting receptors on responsive cells to greater
4 activity.

5 Other aids to weight loss have been proposed, such as substances which prevent the
6 absorption of nutrients from the digestive system, but the value of such approaches is minimal,
7 and in general, the accepted substances of value in weight loss act by modulating
8 neurotransmitter function in the central nervous system or peripherally.

9 Substances which modulate neurotransmitter function in the central nervous system are
10 known to act by increasing the availability of catecholamines, in particular noradrenaline, in
11 certain areas of the brain, thus resulting in perceived suppression of hunger. By suppressing
12 hunger, less food is eaten, and caloric intake is lowered. Examples of such substances include
13 phenylpropanolamine, phentermine and the amphetamines.

14 Substances which act by increasing the availability of 5-hydroxytryptamine (serotonin),
15 on the other hand, are known to increase perceptions of satiety. An example of such a
16 substance is dexfenfluramine.

17 Irrespective of mechanism, substances of either of these types result in reduced food
18 intake. But their use can be attended by various unwanted effects characteristic of interference
19 with other hormone-regulated systems in the body. It has furthermore been noted that the
20 effects of these types of substances are transient, requiring progressively greater dosage to
21 elicit desired effects, until the body finally becomes unresponsive. This progressive decrease in
22 sensitivity is termed tachyphylaxis.

23 More recently, attention has been focused on ephedrine, which was originally thought
24 to suppress the hunger center in the brain. However, during the last 30 years, research has
25 shown that ephedrine acts mainly by stimulating thermogenesis. That is, it increases the

1 metabolic rate and stimulates lipolysis (fat breakdown).

2 The effect of ephedrine on the peripheral metabolic rate is derived from actions on
3 energy-generating tissues combined with stimulation of the release of fat from stored fat
4 depots (adipose tissue). This not only increases the generation of energy but also increases the
5 availability of substrates to be utilized for this energy generation. A valuable consequence of
6 these two actions is the sparing of body protein, which in certain cases, depending on the
7 composition of the diet, may even result in a gain of body protein (anabolic effect).

8 The effects of ephedrine can often be intensified by concomitant use of
9 methylxanthines such as caffeine.

10 Empirical studies have shown that ephedrine, whether as the pure substance or in the
11 form of Ephedra herb:

- 12 (a) Improves rates of weight loss in patients on low calorie diets, spares lean body
13 mass (Pasquali et al., 1992; Kaats and Adelman, 1994), increases the
14 proportion of fat in the weight lost (Astrup et al., 1992b) and prevents the
15 decline in Resting Metabolic Rate usually seen with reduced caloric intake
16 (Astrup et al., 1992b; Astrup and Toubro, 1993).
- 17 (b) Gives results, through increased thermogenesis and stimulation of lipolysis (fat
18 breakdown) at dosage levels below those required to elicit stimulant or hunger
19 suppressant effects (Astrup and Toubro, 1993).
- 20 (c) Shows synergism in the effects on weight loss when combined with caffeine
21 (Daly et al., 1993; Astrup and Toubro, 1993).
- 22 (d) Is not associated with significant adverse effects. Thermogenic effects became
23 more pronounced as treatment continues (Astrup et al., 1985, 1986) while
24 initial adrenergic effects (which are not pronounced) exhibit tachyphylaxis and
25 rapidly disappear (Astrup et al., 1992a).

1 It has even been suggested that ephedrine may be an example of a trace substance that
2 belongs in the human diet, and that it provides an opportunity to attack obesity at a level that
3 is close to causative (Landsberg and Young, 1993).

4 Based on the clinical observations, ephedrine may therefore be considered an ideal
5 pharmacological aid in the treatment of obesity.

6 Though it has some central stimulant effect, and thus mediates suppression of hunger,
7 ephedrine's main mode of action appears to be peripheral and, in part, causative since it offsets
8 the decline in metabolic rate that normally occurs on caloric restriction. The decline in
9 metabolic rate that accompanies caloric restriction, therefore, is well known to those schooled
10 in the art to defeat the initial weight loss benefits associated with caloric restriction. The body,
11 in effect, recognizes the "starvation" period, becomes more efficient in utilizing caloric
12 resources, and simply waits until normal caloric intake is resumed. This explains the "plateau"
13 effect seen in caloric restriction diets. When normal caloric intake is resumed, the body's
14 increased efficiency actually restores the fat lost in the caloric restriction period. This is
15 commonly known as the "yo-yo dieting" effect.

16 The thermogenic action which results from ephedrine's effects on metabolic rate and
17 lipolysis persists throughout its use period, and may intensify as use continues.

18 Ephedrine's classical adrenergic actions, which are undesirable in a weight loss
19 context, cease rapidly due to tachyphylaxis.

20 The classical uses of ephedrine and pseudoephedrine for a variety of conditions are
21 well illustrated by reference to standard works on Pharmacology and Therapeutics. For
22 example, Govoni and Hayes (1985) describe use of ephedrine as a decongestant in allergic
23 rhinitis, sinusitis and chronic asthma (often combined for such indications with theophylline, a
24 methylxanthine closely related to caffeine in structure and effect), in the treatment of
25 narcolepsy, to combat hypotensive states (especially those associated with spinal anesthesia),

1 in the management of enuresis, as adjunctive therapy for myasthenia gravis, as a mydriatic, as
2 temporary support of ventricular rate in Adams-Stokes syndrome, to relieve dysmenorrhoea,
3 and for management of peripheral edema secondary to diabetic neuropathy. Streeten (1975)
4 adds idiopathic edema to the list of conditions where ephedrine (150 - 200 mg per day) has
5 beneficial activity, and other uses verified have included ketotic hypoglycaemia (Court et al.,
6 1974), urological syndromes caused by prostaglandin E₁ (Lowe and Jarow, 1993) and
7 insulin-induced edema (Hopkins et al., 1993). Matthews (1983) discusses the action of
8 ephedrine on the internal sphincter of the bladder and urethra in relation to its use in treating
9 urinary incontinence. Govoni and Hayes (1985) note that maximum parenteral dosage should
10 not exceed 150 mg/day by sub-cutaneous (s.c.), intramuscular (i.m.) or intravenous (i.v.)
11 routes and comment that unwanted effects (all of which are consequent on the pharmacology
12 involved) usually only occur with large doses. The same textbook teaches that
13 pseudoephedrine essentially shares these properties, but is mainly used for relief of rhinitis in
14 doses up to 240 mg/day for adults; Southon and Buckingham (1989) concur that
15 pseudoephedrine and ephedrine have similar pharmacological profiles, but that
16 pseudoephedrine is less potent.

17 Naturally occurring ephedrine is the 1R,2S(-)-erythro form, which is the most active
18 pharmacologically. Pseudoephedrine is the threo form.

19 Acting indirectly, the main action of ephedrine is to elicit release of noradrenaline
20 (norepinephrine) from presynaptic sites. This in turn activates both alpha- and
21 beta-adrenoceptors. The perceived effects on different organs and tissues depend on the
22 relative proportions of the two types of receptors, which mediate different responses. At a
23 basal level, classical pharmacology teaches that alpha-activation results in contraction of
24 smooth muscle (except for intestinal smooth muscle) while beta-activation causes relaxation of
25 smooth muscle and stimulation of the myocardium. But this picture is complicated by the fact

1 that both alpha- and beta-receptors can be subdivided into further types with differing
2 distributions and sensitivities.

3 At a cellular level, activation of beta-receptors results in stimulation of adenylate
4 cyclase. This leads to increases in intracellular levels of cyclic adenosine monophosphate
5 (cAMP). The precise sequence of events (Munson, 1995) is believed to be:

- 6 (1) The beta-agonist binds to the beta-receptor.
- 7 (2) The receptor-agonist complex has high affinity for a stimulatory guanine
8 nucleotide regulatory protein termed the Gs protein, and binds to this protein.
- 9 (3) Formation of the receptor-agonist-Gs complex facilitates the exchange of
10 guanine diphosphate (GDP) for guanine triphosphate (GTP) on the Gs protein.
- 11 (4) The Gs-GTP complex dissociates from the receptor-agonist complex and then
12 interacts with the catalytic subunit of adenylate cyclase, promoting the
13 conversion of adenosine triphosphate to cAMP.
- 14 (5) The cAMP activates a cAMP-dependent protein kinase, which can then
15 phosphorylate a variety of intracellular proteins, ultimately leading to a
16 pharmacological response.

17 Feedback inhibition control is achieved by phosphorylation of receptor proteins, which
18 results in their desensitization.

19 Activation of most alpha-2 receptors has an opposite effect, the first step being
20 inhibition of adenylate cyclase through a guanine nucleotide regulatory protein termed Gi.
21 The Gi protein, by inhibiting the catalytic activity of the adenylate cyclase, leads to a reduction
22 in cellular levels of cAMP, which decreases the activation of the cAMP-dependent protein
23 kinases. However, in some alpha-2 receptors, the Gi protein may act through other
24 mechanisms which have not yet been elucidated, but possibly lead to activation of membrane
25 calcium channels.

1 The alpha-1 receptors have a different mechanism. It does not appear to involve
2 cAMP, but apparently relies instead on diacyl glycerols and inositol-1,4,5-triphosphate.

3 It is readily understood that the beta-receptors can also be further subdivided based
4 upon their mechanism of action. The known subdivision of beta-receptors into beta-1, beta-2,
5 and beta-3 types is of particular interest for this invention since the beta-3-receptor is strongly
6 believed to be responsible for the lipolytic and thermogenic effects of ephedrine while
7 interactions with the other two types of beta-receptors are known to control cardiac effects of
8 ephedrine.

9 Effects on blood pressure, however, are in part due to the stimulation of alpha-2-
10 receptors, where such stimulation produces peripheral vasoconstriction.

11 Central nervous system effects of ephedrine appear to depend on activation both alpha-
12 and beta-receptors (with the exception of beta-3-receptors). The multi-receptor response to
13 ephedrine is also important in explaining observed synergistic effects of caffeine on certain
14 actions of ephedrine.

15 The overall response to ephedrine, reflected in perceived effects, is governed by the
16 distribution of receptors in terms of types and populations. As an example, the activation of
17 beta-receptors causes vasodilation of vessels in the heart and skeletal muscle while
18 simultaneous alpha-2-activation results in vasoconstriction in other vascular beds. This is
19 effectively the classical "fight or flight" response, which together with other metabolic results
20 of adrenoceptor activation is intended to put the body into an optimal state for physical
21 exertion.

22 The metabolic results of adrenoceptor activation also include effects on lipolysis and
23 thermogenesis. In the case of lipolysis, activation of alpha-2-receptors inhibits the process,
24 while activation of beta-receptors (believed to be the beta-3-subtype) stimulates lipolysis and
25 at same time, possibly in part due to increased availability of substrate, induces a thermogenic

1 response. The overall response of the adipose tissue thus depends on the relative proportions
2 of alpha-2 and beta-3 receptors. A high ratio of alpha-2 to beta-3 receptors would produce a
3 comparatively lower thermogenic response than a low ratio. Indeed, the predicted
4 diminishment of thermogenic response associated with increasing proportion of alpha-2
5 compared to beta-3 receptors may explain why some studies of thermogenic responses to
6 ephedrine have found two populations: responders and relative non-responders.

7 Attention has been paid to the unexpected finding that thermogenic properties of
8 ephedrine do not exhibit tachyphylaxis. Landsberg and Young (1993) adopt the position that
9 since the activity of the sympathetic nervous system may be reduced in obesity, improvement
10 of sympathetic nervous system activity to normal levels is physiological rather than
11 pharmacological, and that the use of ephedrine in obese persons does nothing more than
12 restore normal catecholamine function. In this respect, therefore, ephedrine differs in no way
13 from the effects of high protein diets or consumption of foods containing natural thermogenic
14 substances. Lansberg and Young also suggest that ephedrine may be particularly useful in
15 combating the weight gain that usually follows cessation of smoking since smoking cessation
16 is also associated with impaired catecholamine function.

17 Dulloo (1993) concurs with Lansberg and Young's point of view. He notes that at
18 levels compatible with therapeutic doses, ephedrine has little or no direct agonist activity but
19 mediates its effects via endogenous release of noradrenaline and adrenaline. Essentially,
20 therefore, ephedrine does nothing more than increase the efficiency of the system already in
21 place in the body. He notes that this has potential positive implications for ephedrine's use in
22 the treatment of obesity, and also explains some of the obscure clinical observations reported:

- 23 1) The fact that tolerance rapidly develops to the very mild cardiovascular effects of
24 ephedrine, but not to its thermogenic effects, suggests that adrenaline and
25 noradrenaline released by ephedrine activate the beta-3-adrenoceptors.

1 2) The adrenaline released is a preferential agonist for the beta-2-adrenoceptors which
2 stimulate protein synthesis and thus can counteract loss of lean body mass during
3 use of low calorie diets.

4 In this respect, Pasquali et al. (1992) have shown that ephedrine enhances fat loss in
5 diet-restricted obese patients and reduces loss of nitrogen.

6 3) Chronic stimulation of postsynaptic alpha-adrenoceptors by the adrenaline and
7 noradrenaline released in response to ephedrine therapy may activate thyroxine
8 deiodinases, leading to peripheral conversion of T4 (thyroxine) to T3
9 (triiodothyronine), which may, in turn, increase adrenoceptor sensitivity to the
10 thermogenic effects of the catecholamines since T3 is much more active than T4.

11 This mechanism may also partially explain why the thermogenic effect of ephedrine is
12 increased after chronic administration.

13 4) Single dose studies have shown that skeletal muscle and visceral organs contribute
14 most of the thermogenic activity after ephedrine administration, with a minor
15 contribution from adipose tissue. These tissues can all be reactivated and even
16 proliferate in response to chronic catecholamine activation, which may explain the
17 enhanced thermogenesis seen with prolonged ephedrine treatment.

18 Dulloo suggests that ephedrine, with chronic administration, exerts its effects indirectly
19 via adrenaline and noradrenaline and thereby generates its own selectivity for desirable
20 anti-obesity effects. This is accomplished by the down-regulation of adrenoceptor types or
21 subtypes associated with unwanted cardiac or pressor effects and with sustained activation of
22 adrenoceptor types that mediate thermogenesis, lipolysis and protein retention.

23 Arner (1993) approaches the mechanism of ephedrine action from the lipolysis aspect.
24 He notes that catecholamines have both lipolytic and antilipolytic effects, so that at any time
25 there is a balance between these effects. However, it has been suggested that lipid metabolism

/ 2

1 in man is mainly controlled by inhibitory modulators, and adenosine has been shown to reduce
2 the sensitivity of lipolytic beta-adrenoceptors, particularly in subcutaneous fat depots. Several
3 prostaglandins of the E-type are also potent antilipolytic agents. Thus the potentiation of the
4 ephedrine effect by caffeine (which may affect adenosine dynamics) and aspirin (which can
5 inhibit prostaglandin synthesis) may not be restricted to the synaptic gap, but may also extend
6 into the actual fat-mobilizing mechanism.

7 Dulloo (1993) noted that in early investigations of ephedrine use as an anti-obesity
8 agent, attention focused on the main action of ephedrine in reducing appetite (the anorexic
9 effect). It now appears that the thermogenic and lipolytic effects are the main properties that
10 make ephedrine so suitable for use as a weight loss aid. Indeed, significant improvements of
11 rates of weight loss occur at ephedrine dosage levels far below those required to achieve
12 detectable main effects, and increasing dosage to the level at which main effects occur does
13 not necessarily give better rates of weight loss (Daly et al., 1993).

14 While the actions of ephedrine makes it an ideal adjunct for regulating and controlling
15 weight problems, it will be obvious to those skilled in the art that it may also be useful as an
16 ergogenic aid to improve physical performance. The acute action is to increase energy
17 availability and, thus, increase the capacity for physical exertion, while the longer-term actions
18 result in an increase in muscle mass, particularly when combined with appropriate diet
19 programs and training exercises. Indeed, Yang and McElligott (1989) have commented that
20 beta-adrenergic agents may act as very effective anabolic agents when given over long periods
21 of time. Both the beneficial ergogenic effects and the valuable effects on weight loss stem
22 from the combination of the effects of ephedrine on lipolysis and its thermogenic effects. Thus
23 by increasing the rate at which fat is released from body stores (lipolysis) while simultaneously
24 increasing the metabolic rate (thermogenesis), those wishing to lose weight may accelerate the
25 removal of unwanted fat stores.

1 At the same time, since the administration of ephedrine means there is increased
2 availability of substrates (the free fatty acids which are released from the fat stores) for
3 oxidation, the body has access to greater amounts of energy. The body's use of these
4 substrates spares protein that might otherwise be oxidized for energy. Therefore, the use of
5 ephedrine in conjunction with additional favorable circumstances, namely a high protein intake
6 and an exercise program, will also result in increased availability of amino acids for
7 incorporation into protein in the muscle mass.

8 From the foregoing, it will be obvious to those skilled in the art that the agents most
9 suitable for inducing weight loss in those with excess weight, or, for persons of normal weight,
10 increasing energy availability and/or muscle mass, would be sympathicomimetic (adrenergic)
11 agents whose mechanism of action is mainly indirect, resembling that of ephedrine, and whose
12 pharmacokinetics favor retention of the agents in the periphery rather than passage into the
13 brain. Agents whose profiles match these requirements would be less likely to cause central
14 nervous system stimulation under normal conditions of use, but would still possess enough
15 central action to suppress the hunger center. The partition in favor of peripheral tissues would
16 result in increased levels of these agents at the sites of the beta-3-receptors, which mediate
17 lipolysis and thermogenesis. It is also widely believed that sympathicomimetic agents
18 possessing mainly an indirect mechanism of action would be less likely to cause unwanted side
19 effects and less likely to result in addictive situations.

20 Hitherto, the only such agent which has been shown to act in the optimized ideal
21 fashion has been ephedrine itself. Ephedrine has some drawbacks, however. It is primarily
22 provided in pharmaceutical forms which allow quick release in the body for the alleviation of
23 acute respiratory ailments whereas, for the purposes of inducing lipolysis and thermogenesis, a
24 slower release is desirable. Furthermore, many of those who are overweight prefer not to use
25 agents which are presented as drugs. In addition, for a variety of health conditions, such use

1 will often be contraindicated because of the risk of potentially hazardous side effects, which
2 risk could be increased because of the weight problem.

3 Prior to this invention, those wishing to avail themselves of natural products for
4 eliciting weight loss or increasing muscle mass have had no choice other than to use products
5 containing Ephedra herb (Ephedraceae), which contains ephedrine together with related
6 alkaloids. However, because of concerns about the use of Ephedra herb products, many do
7 not avail themselves of this opportunity.

8 The provision of a natural product that acts in the ideal fashion noted above would
9 therefore provide major benefits to those seeking to lose weight or improve their physical
10 fitness, or both, and would be especially useful to those who prefer not to take either drug-like
11 products or natural products containing ephedrine alkaloids.

12 SUMMARY OF THE INVENTION

13 The present invention relates to the discovery that certain plants contain adrenergic
14 amines of the group consisting of synephrine, hordenine, octopamine, tyramine and N-
15 methyltyramine that are useful to assist in weight loss, adding muscle mass, and/or increasing
16 physical performance. More particularly, the present invention relates to the discovery that
17 useful and exploitable levels of these adrenergic amines only occur in plant species of Citrus.

18 In still greater detail, the invention relates to the discovery that these useful levels only
19 occur in parts of the plant that are not normally eaten, including the leaves and bark, or in the
20 fruit in certain stages of maturity. In yet further detail, the invention relates to a composition
21 in which the plant parts are used in various forms to provide therapeutically effective doses of
22 these adrenergic amines and to a composition in which the adrenergic amines are extracted
23 from the plant parts using methods well known to those schooled in the art.

24 In further detail, the invention relates to the use of the composition to stimulate beta-

1 receptors in a predominantly indirect fashion thereby stimulating thermogenesis, increased
2 metabolic rate and lipolysis. In yet additional detail, the invention relates to the use of the
3 composition to control appetite by suppressing hunger.

4 In further detail, the composition of the invention has utility in regulating or treating
5 weight problems as well as increasing vitality, energizing, and in the long term increasing
6 muscle mass.

7 In still further detail, the amounts of the adrenergic amines of this invention needed to
8 be effective can be as low as one mg ingested three times daily, and the low dosage effective
9 range is from one to five mg ingested up to 3 or 4 times daily. Still further, the preferred use
10 of this invention is to administer single doses of from 8 to 30 mg up to 4 times daily, making a
11 total daily dose of about 100 to 120 mg per day.

12 In a further aspect, the present invention relates to a method for weight loss and a
13 method for ergogenesis to aid in improved physical performance and to aid in adding lean
14 muscle mass to the body.

15 An object of the present invention is to provide a composition containing an effective
16 weight control/weight loss amount of at least one of the group of adrenergic amines
17 synephrine, hordenine, octopamine, tyramine and N-methyltyramine.

18 Another object of the present invention is to provide a composition containing an
19 effective amount of at least one of these adrenergic amines to stimulate the addition of lean
20 muscle mass.

21 Yet another object of the present invention is to provide a composition containing an
22 effective amount of at least one of these adrenergic amines to enhance physical performance.

23 Still another object of the invention is a method for promoting weight control, weight
24 loss, enhanced physical performance, and/or the addition of lean muscle mass which includes

1 the step of administering to a subject an effective amount of at least one of the group of five
2 adrenergic amines.

3 Another object of the invention is to obtain the adrenergic amines from the plant
4 material of the genus Citrus, and more specifically from the leaves, bark, unripe fruit, ripe fruit
5 and peel of the species Citrus aurantium and/or Citrus reticulata.

6 In achieving the above and other objects, one feature of the invention is that the
7 composition can be administered in the form of the plant material in a tablet, capsule or other
8 pharmacologically appropriate carrier, in the form of a tea, or in the form without plant
9 material in a tablet, capsule or other pharmacological carrier which contains at least one of the
10 group of five adrenergic amines extracted from the plant material.

11 DESCRIPTION OF DRAWINGS

12 Figure 1 shows the chemical structures of the five alkaloids: synephrine, hordenine,
13 octopamine, tyramine and N-methyltyramine.

14 DETAILED EMBODIMENTS OF THE INVENTION INCLUDING BEST MODE

15 It has now surprisingly been found that agents present in plants other than
16 Ephedraceae may also act as sympathicomimetic agents with suitable mechanisms of action in
17 the body, and use of these plants can therefore result in benefits as outlined with regard to
18 body weight regulation and physical performance.

19 The value of the use of such plants in body weight regulation and physical performance
20 has not been suspected prior to this invention. Though the plants concerned have
21 acknowledged uses and long histories as foods, they have not been used to induce weight loss
22 or for ergogenic purposes. The agents these plants contain have likewise not previously been
23 related to weight loss or ergogenic applications. Furthermore, the agents are generally only
24 present in significant amounts in parts of the plant which are considered as inedible waste for
25 normal consumption, or are only present during certain stages of the growth cycle when the

1 plant would not normally be consumed. While it is true that the plants or their parts harvested
2 during a particular stage of growth have also been used as medicinal herbs or traditional
3 remedies, particularly in the Orient, these uses have also not included applications in either
4 weight loss or for ergogenic purposes, and the uses according to the invention are therefore
5 novel and surprising.

6 The agents contained in the plants which are used in accordance with the invention
7 include synephrine, hordenine, octopamine, tyramine and N-methyltyramine, and they may be
8 found in various species of plants, both food plants and otherwise, as detailed by Wheaton and
9 Stewart (1970), including, but not limited to, Amaryllidaceae, Leguminosae, Liliaceae,
10 Rutaceae, Cyperaceae, Solanaceae and Berberidaceae. Figure 1 shows the chemical structures
11 of synephrine, hordenine, octopamine, tyramine and N-methyltyramine.

12 However, in terms of practical utility, the levels of these agents generally only reach
13 useful values, that is to say levels in excess of 0.1% of dry mass, in certain species of
14 Rutaceae. Furthermore, these useful levels are only achieved during phases of growth where
15 the plant would not normally be used for food, or in parts of the plant which are not
16 considered part of the edible portion such as the leaves. In particular, relatively high levels of
17 synephrine and related substances (such as octopamine, hordenine, tyramine and
18 N-methyltyramine) can be found in various Citrus species, including in particular, but not
19 restricted to, strains of Citrus reticulata (also known as tangerine or mandarin orange), Citrus
20 aurantium (also known as C. florida, C. vulgaris, C. bigaradia, Sour orange, Bitter orange,
21 Seville orange, Neroli orange), Citrus medica, Citrus maxima, Citrus limon, Citrus
22 aurantiifolia, Citrus paradisi, Citrus sinensis and Poncirus trifoliata (trifoliata orange).

23 These various Citrus species have been used, and continue to be used, for a variety of
24 food purposes and for their health benefits, but have hitherto not been revealed as herbs or
25 plants which have value in the treatment of weight problems or for improving physical

1 performance and fitness.

2 Herbs based on Citrus materials have long been used for a variety of medicinal
3 applications unrelated to weight loss. In this respect, for example, the literature discloses a
4 number of Oriental herbs for medicinal applications, including the following:

5 Zhi shi: The immature (dried) fruit of Citrus aurantium is used for the treatment of
6 digestive disorders, to induce diuresis, and as a mucolytic agent to relieve chest congestion
7 (Ou Ming, 1989). It may contain levels of the desired active agents of up to 0.9%. Reid
8 (1986) describes Zhi shi as the unripe fruit of the trifoliolate orange, indicated for digestive
9 disorders and as an expectorant, while Huang (1993) implies that this herb is derived from
10 mature fruits of Citrus aurantium.

11 Zhi Qiao: This herb is also the immature fruit of Citrus aurantium, and is used to treat
12 indigestion and to correct mild ptosis of the uterus (Huang, 1993). Levels of active substances
13 are similar to those in the herb Zhi shi, and the distinction between these two herbs appears to
14 be based on degree of maturity (of the fruit) and the area in which traditionally used.

15 Chen pi: The herb Chen pi is dried peel of Citrus reticulata. This may also be called Jiu
16 Hong, and is used as a digestive aid, antiemetic, antitussive and antifatulant (Huang, op. cit.).
17 The herb also has anti-infective properties (Ou Ming, op. cit.).

18 Qing pi: This herb is immature Citrus reticulata, or in some cases the peel thereof. It is
19 used to treat digestive disturbances and to alleviate pain, as an expectorant, and to relax
20 smooth muscle (Ou Ming, op. cit.).

21 Fo Shou: Also known as Fructus Citri Sarcodactyli, the fruit of Citrus medica var.
22 sarcodactylus, it is used for treatment of digestive disorders, for dysmenorrhea, chest
23 congestion and as an expectorant (Ou Ming, op. cit.).

24 According to Bown (1995), Citrus aurantium and Citrus reticulata are known by
25 different Chinese names in part according to their uses. For example, the whole fruit, peel,

1 unripe fruit, unripe peel and seeds of *C. reticulata* are referred to as "Chen pi" ("dried ripe
2 peel") to treat indigestion, flatulence, vomiting and wet coughs, but as "Qing pi" ("unripe
3 peel") when used to treat liver and gall bladder disorders, bronchial congestion, mastitis,
4 breast cancer, and pain in liver, chest or breasts, while the form "Ju he" (Jiu hong; normally
5 the seeds) is used to treat lumbago, orchitis and mastitis.

6 In Western traditional medicine, Wichtl (1994) describes use of the mature or
7 immature fruit of *Citrus limon* for the treatment of digestive problems and phlebitis, and notes
8 that the flowers of *Citrus aurantium* and occasionally *Citrus sinensis* are also used for their
9 sedative effects. Wichtl also reports that dried peel of *Citrus aurantium*, or the dried whole
10 immature fruit, is used in gastrointestinal remedies, tonics, roborants and cholagogues. Grieve
11 (1992) describes use of lemon juice for the treatment of rheumatism, and of the oils from
12 various oranges for alleviation of chronic bronchitis. Font Quer (1982) refers to the
13 antispasmodic and hypnotic properties of *Citrus aurantium* flowers, and to the use of the dried
14 peel as a gastric tonic and antifatulent.

15 Numerous other standard textbooks of herbology refer to *Citrus* material of various
16 types and its use for the alleviation of gastric disorders. However, neither the use of such
17 materials to induce weight loss nor their use to increase physical performance or muscle mass
18 are described, and these uses are therefore surprising, novel and not anticipated.

19 The active agents synephrine, hordenine, octopamine, tyramine and N-methyltyramine
20 are known to be adrenergic agents, and synephrine is still used under the synonym oxedrine in
21 some countries for the treatment of hypotension (Reynolds, 1982). However, apart from
22 occasional use of tyramine as a diagnostic agent in suspected cases of pheochromocytoma,
23 their use has been abandoned in favor of newer, synthetic adrenergic agents, and no indication
24 of their value in weight loss or physical performance can be found in the literature. Their
25 valuable properties in these respects are therefore unanticipated, surprising and novel.

1 The Citrus material used in accordance with the invention may consist of any portion
2 of the plant which contains useful amounts of the agents as defined above, which may vary
3 depending on the species, stage of growth, season, and agronomic conditions. For example,
4 leaves of Citrus reticulata are preferred to other parts of this plant, and may show levels of
5 synephrine and related alkaloids of 1.1% or more, based on dry matter, while the peel of the
6 immature fruit shows levels of only 0.2% - 0.4%. In the case of Citrus aurantium, the
7 preferred form is the whole immature fruit of the amara variety, though the peel of the mature
8 fruit can also be used. In both Citrus aurantium cases, total levels of 0.2% - 0.9% of
9 synephrine and the related agents are regularly found. Both the peel and the whole fruit
10 (immature or mature) of the dulce variety also have utility, though levels generally do not
11 exceed 0.4%.

12 Though it is possible to use a variety of Citrus materials in accordance with the
13 invention, it is more convenient to utilize Citrus materials which already exist in appropriate
14 form and which are generally available as traditional herbs and remedies. For example, the
15 agents are present in the residues remaining after steam distillation of Citrus aurantium fruits
16 to obtain the essential oils. In this respect, various Chinese herbs, or materials from other
17 geographic locations prepared in the same way, are particularly useful, as are Citrus reticulata
18 leaves.

19 The Chinese herbs which are most convenient for use are:

20 o Zhi shi, which is the immature (dried) fruit of Citrus aurantium, but may also
21 consist of the peel of the mature fruit, or the peel of either. This herb contains 0.2% - 0.9%
22 total alkaloids with synephrine predominating.

23 o Zhi Qiao, which is also the immature fruit of Citrus aurantium has levels of
24 active substances similar to those in the herb Zhi shi.

25 o Chen pi, the dried peel of Citrus reticulata, may also be called Jiu Hong. This

1 herb contains 0.1% - 0.4% total alkaloids.

2 o Qing pi is the dried immature *Citrus reticulata*, or in some cases the peel
3 thereof. This herb contains 0.1% - 0.4% total alkaloids.

4 o Fo Shou, also known as *Fructus Citri Sarcodactyli*, is the fruit of *Citrus medica*
5 var. *sarcodactylus*. This herb contains 0.1% - 0.3% total alkaloids.

6 In addition to the above, peel of the mature or immature fruit of *Citrus limon* may
7 conveniently be obtained, since it is also an item of commerce, while tangerine leaves are also
8 readily obtained at certain seasons.

9 In a preferred embodiment of the invention, therefore, material from *Citrus* species is
10 given to humans by the oral route, either concurrently with caloric restriction or in the absence
11 of caloric restriction, for the purpose of controlling body weight. The invention works
12 predominantly by increasing thermogenesis, that is, by increasing the metabolic rate and
13 facilitating lipolysis. The invention also exhibits a hunger-suppressing effect which may
14 become more obvious in higher doses as well as in individuals in which the active agents pass
15 the blood-brain barrier more readily. Thus, most users will benefit mainly from the
16 thermogenic effect and additionally may also experience mild suppression of hunger such that
17 both mechanisms operate simultaneously, thereby providing an added benefit. In addition, the
18 said material can be given to humans, either with or without a high protein diet (>1.25 gm
19 protein/kg ideal body weight/day), for the purpose of increasing physical performance in the
20 short-term and to increase muscle mass and functionality in the long term.

21 The *Citrus* material so used is selected for its content of active agents as defined above
22 such that the total amount of *Citrus* material ingested provides a sufficient amount of the
23 active agents to achieve the desired effects. In this respect, the preferred embodiment
24 consisting of a sufficient amount would be defined as at least 0.04 mg of active agents per
25 kilogram ideal body weight per dose at any one time. In practical terms this corresponds to

1 2.8 mg for a person of 70 kg ideal body weight.

2 Ingestion of active agents in the range of 0.01 mg to 0.10 mg per kilogram of ideal
3 body weight per serving will be effective in accomplishing the desired goal of weight loss,
4 though more preferred is a range of 0.02 mg to 0.06 mg per kilogram of ideal body weight,
5 and most preferred is 0.05 mg per kilogram of ideal body weight. Though ingestion of larger
6 amounts of the agents will not diminish the beneficial effects, the effects may not necessarily
7 be increased while the possibility of side-effects due to activation of other adrenergic systems
8 would be increased. Thus, at an intake level of 1 mg per kilogram of ideal body weight per
9 serving, it is possible that the adrenergic receptors in the cardiovascular and central nervous
10 system could be activated thereby resulting in increases in blood pressure as well as
11 tachycardia, nervousness, agitation, tremors, and insomnia.

12 Daily intake of the active agents for effective body weight loss according to the
13 invention is in the range of 0.16 mg to 1 mg per kilogram of ideal body weight. Thus, an adult
14 male whose desired body weight is 176 pounds would lose weight according to this invention
15 with servings of 4 mg, with total daily intake in the amount of 32 mg.

16 In this context, the active agents are deemed to be any one or more of synephrine,
17 hordenine, octopamine, tyramine and N-methyltyramine, whereby the sufficient amount may
18 be any one singly, or a combination of the agents that together provide a sufficient amount.

19 Because levels of the said agents are often relatively low and variable, and also because
20 in their natural state the agents are associated with parts of the plant that are unpalatable, it
21 may be difficult to achieve an intake of Citrus material in a volume sufficient to provide a
22 suitable amount of the agents as defined above.

23 To enhance edibility, the Citrus material may be consumed as a concentrate or as an
24 extract in either dry or liquid form. By producing a concentrate or extract, the levels of the
25 agents in the material are increased to an effective level. There are several ways readily known

1 to those schooled in the art which permit production of a concentrate or extract. The Citrus
2 material may be enriched in the agents, for example, by extraction of the Citrus material with
3 water, dilute acids or certain organic solvents, including mixtures thereof with water, followed
4 by drying on a carrier of unconcentrated Citrus material, or by drying on a carrier of another
5 suitable material. Such a suitable material may include, but is not limited to, maltodextrins,
6 starch, protein or other carrier material, the nature of which will be obvious to those skilled in
7 the art of manufacturing extracts of botanical materials. The Citrus material may also be
8 extracted and concentrated without drying to give a liquid extract that can also be consumed.

9 When prepared as an extract or concentrate, the Citrus material is preferably dried so
10 that it may be given in the form of tablets, capsules, powders or other convenient form, or it
11 may be admixed with foods or special food products, or it may be given in the form of a tea or
12 tisane. When prepared as a liquid extract, the Citrus material may be consumed as drops, or
13 from an appropriate liquid measure (teaspoon), or it may be admixed with other liquids or
14 incorporated into solid food products. Preparation as an extract or concentrate permits
15 production of standardized amounts of the active agents so as to produce a less variable
16 response in terms of desired weight loss and/or the desired increase in muscle mass.

17 If it is not prepared as an extract or concentrate, the Citrus material may be given
18 fresh, but is preferably dried so that it may be given in the form of tablets, capsules, powders
19 or other convenient form, or it may be admixed with foods or special food products, or it may
20 be given in the form of a tea or tisane.

21 For example, the dried leaves of Citrus reticulata var. Blanco may be filled into tea
22 bags to give a refreshing vitalizing drink that enervates and suppresses hunger for long
23 periods, while dried immature fruits of Citrus aurantium var. amara are best milled to a fine
24 powder and either tabletted or filled into capsules for repeated oral administration to achieve
25 similar effects over a period of weeks or months.

1 The Citrus materials may also be admixed with other ingredients to form the basis of a
2 dietary product, which may either be a nutritional drink or a nutritional bar. One such
3 nutritional bar can provide 15 grams of protein, 26 grams of carbohydrate and 5 grams of fat
4 in addition to a quantity of the Citrus material. Such products may thus be used as meal
5 replacements by those seeking to lose weight, or by those requiring nutritional support during
6 sporting activities, whereby the benefits of the Citrus material are supported by the nutritional
7 content of the food product.

8 The Citrus material, either in the form of an extract or as the natural material, may also
9 be given in combination with other herbs that possess beneficial effects for humans, and
10 particularly in respect to weight loss or improvements in physical performance. In this
11 connection, suitable herbs and foods include those herbs and foods that contain
12 methylxanthines such as caffeine, theobromine and theophylline, which by virtue of their
13 inhibition of the enzyme phosphodiesterase may potentiate the thermogenic actions of the
14 Citrus materials and increase the actions at the level of the beta-3-receptors. At the same time,
15 the actions of methylxanthines on alpha-receptors may serve to reduce or eliminate any
16 unwanted cardiovascular effects, such as peripheral vasoconstriction and increase in blood
17 pressure, that would be undesirable within the context of weight loss or improved physical
18 performance. Suitable herbs and foods in this respect include, but are not limited to, Paullinia
19 cupana (Guarana), Ilex paraguariensis (Maté), Cola nitida, Cola acuminata, Camellia sinensis
20 (Tea), Coffea arabica (Coffee) and Theobroma cacao (Cocoa), whereby the herb or food may
21 be used as the natural material or an extract thereof. In such cases, the herb so chosen is
22 admixed with the Citrus material in a suitable form to provide a solid or liquid dosage unit.

23 The invention is further exemplified and illustrated by the following examples which
24 are not limiting.

1 Example 1:

2 Tea-bags containing each 2.5 grams dried tangerine leaves (*Citrus reticulata* var.
3 Blanco) were prepared. The tangerine leaves had a synephrine content of 1.1% and
4 approximately 0.5% of the related alkaloids, which did not resolve completely on HPLC
5 analysis, thus providing a total amount of 40 mg of alkaloids per serving. The tea bags were
6 infused for 5 minutes in hot water at 85°C, and the resulting tisane was given to 5 volunteers
7 (GL, RE, NS, CS, PS). All volunteers reported increased energy, which in one case was
8 perceptible as agitation and nervousness, persisting for 8 - 10 hours. During this period,
9 subjects did not feel hungry and refrained from eating snacks or meals.

10 Example 2:

11 A Zhi shi powder (*Citrus aurantium*, var. amara, whole immature fruit dried) was
12 obtained from a Chinese source. This powder contained 0.49% synephrine and approximately
13 0.5% of the related alkaloids. It was mixed with 2% magnesium stearate and 1% silicon
14 dioxide to confer flowability and filled into white size 0 snap-fit capsules. Capsule fill weight
15 was 490 mg, plus or minus 5%. Subjects DJ and HAF then took 3 capsules 3 times daily for
16 four weeks, corresponding to an intake of 14 mg total alkaloids per serving, or 42 mg per day,
17 without deliberate restriction of food intake. Subject DJ, initial weight 105.4 kg, showed a fall
18 in body weight to 100.9 kg, while the body weight decrease in subject HAF was from 74.5 kg
19 to 72.0 kg. Upon ceasing use of capsules, subjects showed slow increases in body weight at a
20 rate of approximately 0.4 kg per week.

21 Example 3:

22 A portion of the Zhi shi powder used in Example 2 was concentrated by extraction
23 with water and redrying on a portion of the original material to give a dry extract with a total
24 alkaloid content of 3.77%, of which approximately 1.9% was synephrine itself. This material
25 was filled into capsules as in Example 2 to provide a product with 18 mg alkaloids of the

1 synephrine group per capsule. Subjects DJ and HAF then took 1 capsule of this product 3
2 times daily for four weeks, providing a daily intake of 54 mg synephrine and related alkaloids.

3 During this time, subject DJ, without deliberate restriction of food intake, showed a decrease
4 in weight from 93.2 kg to 90.4 kg, but subject HAF had to cease use after the first day
5 because of unpleasant sensations of agitation and nervousness.

6 Example 4:

7 Two batches of nutrition bars were prepared using the Thermobar concept, that is,
8 chocolate-flavored taffy bars weighing 57 grams providing 15 grams protein, 26 grams
9 carbohydrate, 5 grams fat and 200 kilocalories. One batch of the bars additionally contained
10 0.5 grams of the extract from Example 3 per bar. Subject RE was given two of the placebo
11 bars. Respired gases were collected by the Douglas bag technique starting 30 minutes before
12 ingestion of the bars and for a 90 minute period thereafter. The respiratory quotient (RQ) was
13 initially 0.78 and rose to 0.86 during the 60 minutes after bar consumption. Two days later
14 following the identical protocol, the subject consumed two of the bars containing the Zhi shi
15 extract, corresponding to about 38 mg of synephrine and related alkaloids; respiratory quotient
16 rose from 0.77 to 0.89 during the 60 minutes after bar consumption. Conversion of these
17 results of indirect calorimetry to energy expenditure showed that the Zhi shi extract had
18 increased the energy expenditure and the thermic response to the food by about 2.5%, thus
19 indicating a thermogenic effect of the ingested alkaloids.

20 Example 5:

21 A group of 9 women, of whom 6 were mildly obese, 1 moderately obese and 2 slightly
22 overweight, with Body Mass Indices ranging from 23.1 to 33.4 were placed on a diet
23 providing 900 - 1000 kilocalories per day, more than 100 g protein per day and less than 100 g
24 carbohydrate per day. From day 8 of this dietary regime, they were additionally given a

product in capsules identified as "Herbal Balance Z-4", providing each 325 mg of a dried Citrus aurantium (immature whole fruit) extract, 125 mg of a dried Paullinia cupana extract, 5 mg of Ginkgo biloba extract and 5 mg Panax ginseng extract. They were instructed to take 1 - 3 capsules 1 - 3 times per day, and to remain at a comfortable intake level within these parameters; 2 subjects stabilized at 2 capsules per day, 2 at 3 capsules per day, 2 at 4 capsules per day and 3 at 5 capsules per day. The Citrus aurantium extract contained 4.14% total alkaloids by HPLC, with approximately 2.8% as synephrine itself. The daily use recorded thus corresponds to a total alkaloid intake of 27.0 to 67.5 mg.

Starting weights, weights at day 8, and weights at day 15 were determined. In addition, each subject completed a daily mood, appetite and satiety rating questionnaire.

Subject	Age:	Height (m)	BMI:	Weights (kg):		
				Day 0	Day 8	Day 15
HS	38	1.57	24.9	61.4	60.5	57.3
GA	40	1.67	29.7	82.7	81.6	80.0
CB	25	1.65	23.1	62.7	62.7	60.0
CA	46	1.61	26.7	69.1	68.2	64.5
LG	30	1.60	25.7	65.8	64.5	62.8
AW	41	1.64	33.4	90.1	88.6	85.4
AEM	31	1.67	23.8	66.6	65.4	64.1
CRT	23	1.73	25.9	77.5	76.8	74.5
LB	29	1.62	26.0	68.2	67.3	65.4

A statistical analysis showed a mean of 0.94 kg during the first week when no product was given and 2.40 kg during the second week when product was taken, the Z-4 product significantly increased weight loss ($P < 0.05$) during the second week.

STATISTICAL ANALYSIS

Means \pm standard deviations:

	Body Weight (kg)	Weight Loss (kg):
Day 0	71.57 \pm 9.75	
Day 8	70.62 \pm 9.54	0.94 \pm 0.43
Day 15	68.22 \pm 9.54	2.40 \pm 0.84

Full data on body weight indicated:

Day:	Mean:	SD:	Median:	Minimum:	Maximum:
0	71.57	9.75	68.20	61.40	90.10
8	70.62	9.54	67.30	60.50	88.60
15	68.22	9.54	64.50	57.30	85.40

Full data on weight loss indicated:

Day:	Mean:	SD:	Median:	Minimum:	Maximum:
8	0.94	0.43	0.90	0.00	1.50
15	2.40	0.84	2.30	1.30	3.70

This result is particularly interesting, since part of the observed weight loss during the first week was due to water loss as a result of changes in electrolyte and water balance (adaptation to reduced caloric intake).

The foregoing description represents the best mode presently known to the inventor of practicing the invention, and is not intended to limit the scope of the present invention which is set forth in the following claims. Likewise, those skilled in the art, given the present disclosure, will recognize that equivalent methods and materials may also be used in practicing the invention. It is contemplated that such equivalents are also within the scope of the present invention.